EDITORIALS

Cigarettes, Sex, and Lung Adenocarcinoma

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For the past 50 years, the winds of change have been blowing through the epidemiology and demographics of lung cancer. Worldwide changes in the incidences, sex ratios, smoking associations, and pathologic types of lung cancer have been dramatic. Such rapid, extensive, and global changes are unprecedented and have not been observed for any other major form of human cancer. In this issue of the Journal, Thun et al. *(1)* explore the reasons for one of these changes, the explosive rise in the relative and absolute incidences of lung adenocarcinoma in both sexes.

The most common cancer in the world today is lung cancer *(2)*. Although the smoking epidemic has been steadily decreasing in some parts of the world, it continues to spread at an accelerated rate in underdeveloped and developing countries *(3–6)*. In the United States, lung cancer is the most common cause of cancer deaths in both sexes, and its incidence has been rising for at least 50 years *(7)*. While major geographic differences exist, in all countries the incidence of lung cancer is greater in men than in women *(3)*. However, in Tasmania, for example, the age-standardized lung cancer incidence rates in 25–44-year olds for the 10-year period from 1983 through 1992 were much higher among women than among men *(8)*. This reflects a dismal fact, i.e., although the efficacy of antismoking campaigns is finally beginning to result in lower cancer incidences in some parts of the world, including among white men in this country, increased smoking by young women in many parts of the world (including the United States and Tasmania) has prevented such a decrease in women.

Lung cancer consists of four major histologic subtypes. Most centrally located squamous cell and small-cell carcinomas arise from epithelial cells that line the surfaces of the centrally located large- and medium-sized bronchi. In contrast, most adenocarcinomas arise from epithelial cells in the peripherally located bronchioles and alveoli. The large-cell carcinomas probably represent undifferentiated tumors or poorly differentiated examples of the other major types. There are important differences between the molecular changes present in adenocarcinomas and other lung cancers, both in number and in type *(9,10)*, indicating different pathogenetic mechanisms. Although preneoplastic changes in the central airways are well documented for squamous cell carcinoma and are strongly smoking associated *(11)*, preneoplastic changes accompanying adenocarcinomas are rarer and more controversial *(12)*. Of great interest, recent findings *(13,14)* indicate that clonal genetic alterations of allele loss at sites of known or putative tumor suppressor genes are found in the bronchial epithelium of most current smokers and these alterations persist for many years after smoking cessation. Similar changes have been described in the peripheral airway cells of patients with lung cancer *(15)*.

Lung cancer is closely associated with smoking, and tobacco smoke contains many mutagenic and carcinogenic chemicals *(16)*. Results from molecular epidemiology *(17)* and laboratory *(18,19)* studies suggest that point mutations in tumor suppressor genes such as TP53 (also known as p53), which are inactivated in all types of lung cancer, and dominant oncogenes such as mutated K-ras genes, which are present in a subset of adenocarcinomas, may be specific both for the type of tumor and for the critical environmental exposure. Thus, the lungs of smokers contain benzo[*a*]pyrene diol-epoxide-guanine DNA adducts, which are associated with the type of mutations found in the K-ras or p53 genes (G to T transversions).

Shifts in histologic type as well as differences in sex and race distribution have accompanied the increased incidence of lung cancers. Several studies *(3,4,7,20)*, including the one in this issue of the Journal *(1)*, indicate that lung cancer incidence increased more rapidly, relative to the other smoking-associated cancers, in women than in men *(1)*. In recent years, lung adenocarcinoma, a rare tumor type at the turn of the century, has replaced squamous cell carcinoma as the most frequent histologic type for all sexes and races combined *(7)*. The adjusted odds ratios for major lung cancer types, especially adenocarcinoma, are consistently higher for women than for men at every level of exposure to cigarette smoke *(21)*. Furthermore, this sex difference cannot be explained by differences in baseline exposure, smoking history, or body size, but it is likely due to the higher susceptibility to tobacco carcinogens in women *(21)*. As discussed by Thun et al. *(1)*, the reasons for the explosive rise in the incidence of adenocarcinoma include diagnostic advances, such as computerized scans and fine-needle aspirations that permit identification of peripherally arising adenocarcinomas, altered criteria and tests for pathologic typing, and changing patterns of cigarette smoking and exposure. Thun et al. *(1)* examined data from the Connecticut Tumor Registry and two

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American Cancer Society studies and confirmed that adenocarcinoma in Connecticut increased nearly 17-fold in women and nearly 10-fold in men from 1959 through 1991. The increase followed a clear birth cohort pattern, paralleling sex and generational changes in smoking more than diagnostic advances. The authors conclude that increases in lung adenocarcinoma since 1950 are more consistent with changes in smoking behavior and cigarette design than with diagnostic advances or changes in histologic interpretation. Other studies conducted in the United States *(22)* and abroad *(23)* have reached similar conclusions. Recent evidence *(24)* indicates that smoking is a major risk factor for adenocarcinomas of the esophagus and gastric cardia, whose incidences have risen steeply over the last few decades.

What can we learn from the careful study by Thun et al. *(1)*? The clear documentation that the rising incidence of adenocarcinoma, the major histologic type of lung cancer in this country, is smoking related has tremendous impact for smoking cessation and prevention efforts, especially since the link between them previously has been regarded as weak. These dramatic findings indicate the importance of epidemiology and population-based studies and their enormous contributions to cancer medicine. The study would have been difficult without data from the Connecticut Tumor Registry and the American Cancer Society prevention studies. The results presented underscore the importance of collection of such data as a public health measure that local, state, and federal governments must actively support. Recent improvements in computing, communication, informatics, and data analyses should make epidemiologic studies easier to perform, more useful, and more accessible.

What are the possible mechanisms by which changes in smoking behavior and cigarette design result in the increasing incidence of adenocarcinoma? Although cigarette consumption has gradually decreased in the United States from a high of about 3800 cigarettes per adult per year in 1965 to about 2800 cigarettes in 1993 *(5)*, deaths from lung cancer have reached a high among both men and women and, as previously mentioned, have been accompanied by dramatic rises in the relative and absolute incidence of adenocarcinoma, especially among women. One factor is the decrease in average delivery from cigarettes of nicotine and tar from about 2.7 and 38 mg, respectively, in 1955 to 1.0 and 13.5 mg, respectively, in 1993. Other major factors for the reduced emissions in smoke relate to changes in the composition of the cigarette tobacco blend and general acceptance of cigarettes with filtertips; filtertip cigarettes constitute 97% of all cigarettes currently sold. Another important change in the composition of the tobacco blend of cigarettes made and sold in the United States is a substantial increase in nitrate content (0.5% to 1.2%–1.5%), which raises the yields of nitrogen oxides and *N*-nitrosamines in the inhaled smoke *(5)*. The original high-tar nonfilter cigarettes were too toxic to permit deep inhalation by smokers; for the smokers of such cigarettes, the formation of eddies of smoke around bifurcations of the bronchi probably resulted in the deposition of particulate materials, eventually leading to the development of centrally located carcinomas. However, smokers of more recently manufactured cigarettes compensate for the low delivery of nicotine by inhaling the smoke more deeply and by smoking more intensely *(5)*. Thus, the peripheral lung, the site of origin of most adenocarcinomas, is exposed to increased amounts of smoke carcinogens *(5)*. All of these factors, the more intense smoking, the deeper inhalation of the smoke, and the increased yields of *N*-nitrosamines in the smoke of low-yield cigarettes are considered major contributors to the drastic increase in lung adenocarcinoma among cigarette smokers in recent years *(5)*. Paradoxically, the widespread use of "safer and gentler" cigarettes may have added fuel to the present lung cancer epidemic.

With 1.5 times more U.S. women dying of lung cancer than breast cancer *(25)*, strategies for cancer prevention for women will need to include lung cancer. In the past, major studies [e.g., *(26)*] for lung cancer prevention and early diagnosis have excluded women. This situation can no longer be justified or tolerated. For early diagnosis and chemoprevention studies, we need to devise improved methods to examine the peripheral lung more efficiently. The new generation of computed tomography scanners may aid the early diagnosis of peripheral lesions, and improved invasive and noninvasive methods may be able to sample such lesions. However, new developments in molecular diagnosis, such as oncogene mutations in exfoliated cells from the central *(27)* and peripheral *(28)* airways, are needed. Several clinical chemoprevention trials *(29,30)* in this and other countries are being conducted to determine whether pathologic and molecular preneoplastic changes in the lungs of smokers can be reversed.

However, one important aspect of lung adenocarcinoma remains a mystery. While all forms of lung cancer are smoking associated, the association is weakest for adenocarcinoma. Adenocarcinoma is the most common form of lung cancer present in young persons, women of all ages, lifetime nonsmokers, and long-term former smokers *(7,31–33)*. In some Asian countries, where smoking among women is relatively uncommon, the high incidence of adenocarcinoma cannot be attributed to smoking *(3,33)*. The patterns and types of oncogene mutations differ in lung cancers arising in smokers and nonsmokers *(18,34)*, indicating differences in pathogenesis. While exposure to volatile cooking oils have been implicated as a cause of lung cancers arising in nonsmoking Asiatic women, no single factor can explain all of the observations *(3,35,36)*. Clearly, the devil we know is easier to deal with than the devil we do not know.

References

(1) Thun MJ, Lally CA, Flannery JT, Calle EE, Flanders WD, Heath CW Jr. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997;89:1580–6.

(2) Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer 1993;54:594–606.

(3) Parkin DM, Sasco AJ. Lung cancer: worldwide variation in occurrence and proportion attributable to tobacco use. Lung Cancer 1993;9:1–16.

(4) Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr, Doll R. Mortality from smoking worldwide. Br Med Bull 1996;52:12–21.

(5) Wynder EL, Muscat JE. The changing epidemiology of smoking and lung cancer histology. Environ Health Perspect 1995;103 Suppl 8:143–8.

(6) Rachtan J, Sokolowski A. Risk factors for lung cancer among women in Poland. Lung Cancer 1997;18:137–45.

(7) Travis WD, Travis LB, Devesa SS. Lung cancer [published erratum appears in Cancer 1995;75:2979]. Cancer 1995;75(1 Suppl):191–202.

(8) Dwyer T, Blizzard L, Shugg D, Hill D, Ansari MZ. Higher lung cancer rates in young women than young men: Tasmania, 1983 to 1992. Cancer Causes Control 1994;5:351–8.

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(9) Sato S, Nakamura Y, Tsuchiya E. Difference of allelotype between squamous cell carcinoma and adenocarcinoma of the lung. Cancer Res 1994;54: 5652–5.
(10) Mitsudomi T, Viallet J, Mulshine JL, Linnoila RI, Minna JD, Gazdar AF. Mutations of ras genes distinguish a subset of non-small-cell lung cancer cell lines from small-cell lung cancer cell lines. Oncogene 1991;6:1353–62.
(11) Auerbach O, Stout AP, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to smoking and cancer of the lung. N Engl J Med 1961;265:253–67.
(12) Kitamura H, Kameda Y, Nakamura N, Inayama Y, Nakatani Y, Shibagaki T, et al. Atypical adenomatous hyperplasia and bronchoalveolar lung carcinoma. Analysis by morphometry and the expressions of p53 and carcinoembryonic antigen. Am J Surg Pathol 1996;20:553–62.
(13) Mao L, Lee JS, Kurie JM, Fan YH, Lippman SM, Lee JJ, et al. Clonal genetic alterations in the lungs of current and former smokers. J Natl Cancer Inst 1997;89:857–62.
(14) Wistuba II, Lam S, Behrens C, Virmani AK, Fong KM, LeRiche J, et al. Molecular damage in the bronchial epithelium of current and former smokers. J Natl Cancer Inst 1997;89:1366–73.
(15) Hung J, Kishimoto Y, Sugio K, Virmani A, McIntire DD, Minna JD, et al. Allele-specific chromosome 3p deletions occur at an early stage in the pathogenesis of lung carcinoma [published erratum appears in JAMA 1995;273:1908]. JAMA 1995;273:558–63.
(16) Carbone D. Smoking and cancer. Am J Med 1992;93:13S–17S.
(17) Vineis P, Caporaso N. Tobacco and cancer: epidemiology and the laboratory. Environ Health Perspect 1995;103:156–60.
(18) Westra WH, Slebos RJ, Offerhaus GJ, Goodman SN, Evers SG, Kensler TW, et al. K-ras oncogene activation in lung adenocarcinomas from former smokers. Evidence that K-ras mutations are an early and irreversible event in the development of adenocarcinoma of the lung. Cancer 1993;72:432–8.
(19) Denissenko MF, Pao A, Tang MS, Pfeifer GP. Preferential formation of benz[*a*]pyrene adducts in lung cancer mutational hotspots in P53. Science 1996;274:430–2.
(20) Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. Cancer Res 1994;54:5284–95.
(21) Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst 1996;88:183–92.
(22) Ernster VL. The epidemiology of lung cancer in women. Ann Epidemiol 1994;4:102–10.
(23) Levi F, Franceschi S, La Vecchia C, Randimbison L, Te VC. Lung carcinoma trends by histologic type in Vaud and Neuchatel, Switzerland, 1974–1994. Cancer 1997;79:906–14.
(24) Gammon MD, Schoenberg JB, Ahsan H, Risch HA, Vaughan TL, Chow WH, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89: 1277–84.
(25) Anonymous. Cancer facts and figures–1997. Atlanta: American Cancer Society Publication, 1997.
(26) Berlin NI, Buncher CR, Fontana RS, Frost JK, Melamed MR. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Results of the initial screen (prevalence). Early lung cancer detection: introduction. Am Rev Respir Dis 1984;130:545–9.
(27) Mao L, Hruban RH, Boyle JO, Tockman M, Sidransky D. Detection of oncogene mutations in sputum precedes diagnosis of lung cancer. Cancer Res 1994;54:1634–7.
(28) Mills NE, Fishman CL, Scholes J, Anderson SE, Rom WN, Jacobson DR. Detection of K-ras oncogene mutations in bronchoalveolar lavage fluid for lung cancer diagnosis [published erratum appears in J Natl Cancer Inst 1995;87:1041–3]. J Natl Cancer Inst 1995;87:1056–60.
(29) Greenwald P, Kelloff G, Burch-Whitman C, Kramer BS. Chemoprevention. CA Cancer J Clin 1995;45:31–49.
(30) Lippman SM, Clayman GL, Huber MH, Benner SE, Hong WK. Biology and reversal of aerodigestive tract carcinogenesis. Cancer Treat Res 1995; 74:89–115.
(31) Limsila T, Mitacek EJ, Caplan LS, Brunnemann KD. Histology and smoking history of lung cancer cases and implications for prevention in Thailand. Prev Med 1994;23:249–52.
(32) Muscat JE, Wynder EL. Lung cancer pathology in smokers, ex-smokers and never smokers. Cancer Lett 1995;88:1–5.
(33) Choi JH, Chung HC, Yoo NC, Lee HR, Lee KH, Choi W, et al. Changing trends in histologic types of lung cancer during the last decade (1981–1990) in Korea: a hospital-based study. Lung Cancer 1994;10:287–96.
(34) Gao HG, Chen JK, Stewart J, Song B, Rayappa C, Whong WZ, et al. Distribution of p53 and K-ras mutations in human lung cancer tissues. Carcinogenesis 1997;18:473–8.
(35) Zhang ZF, Sarkis AS, Cordon-Cardo C, Dalbagni G, Melamed J, Aprikian A, et al. Tobacco smoking, occupation, and p53 nuclear overexpression in early stage bladder cancer. Cancer Epidemiol Biomarkers Prev 1994;3: 19–24.
(36) Ernster VL. Female lung cancer. Annu Rev Public Health 1996;17:97–114.

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